Clinical trial results:
A multi-center, double-blind, randomized, placebo-controlled, dose-finding study in patients with active rheumatoid arthritis incompletely controlled on stable MTX doses to investigate efficacy and safety of SC BT061

Summary

EudraCT number	2010-018485-24
Trial protocol	CZ ES DE HU LV
Global end of trial date	16 October 2013

Results information

Result version number	v1 (current)
This version publication date	25 December 2021
First version publication date	25 December 2021

Trial information

Trial identification

Sponsor protocol code	979

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01481493
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biotest AG
Sponsor organisation address	Landsteinerstr. 5, Dreieich, Germany, 63303
Public contact	Daniela Zipp, Biotest AG, +49 6103 801 255 , daniela.zipp@biotest.com
Scientific contact	Daniela Zipp, Biotest AG, +49 6103 801 255 , daniela.zipp@biotest.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 August 2013
Global end of trial reached?	Yes
Global end of trial date	16 October 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Is to investigate dose-response information on efficacy.

Primary efficacy variable is ACR20 (at Week 13).

Protection of trial subjects:

The patient had to give written consent to participate in the trial by signing and dating the informed consent form (ICF) before screening. Any new and relevant information that evolved during the course of the trial concerning the investigational medicinal product (IMP), alternative treatments, or the risk/benefit ratio was communicated to the patient.
After SC administration the patient was asked to stay at the investigational site for at least 2 hours to cover the potential risk of a type I hypersensitivity reaction. Therefore, intensive care measures had to be available. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur.
After administration of the last dose of the IMP patients were observed for a 12-week follow-up period on a regular outpatient basis. All these patients had in addition a safety follow-up visit at Week 24.
Treatment is discontinued if at least one of the following three criteria are met for two consecutive weekly assessments.
• CD3CD4 cell count ≤ 200 cells/µl or
• CD3CD4 cell count < 50% of individual baseline count or
• Total lymphocyte count < 50% of individual baseline count
The treatment will be discontinued for male patients in case:
• TSH, follicle-stimulating hormone (FSH), luteinizing hormone (LH) or testoste-rone levels are outside the normal range and
• The investigator assesses these changes as compared to baseline as clinically relevant for 2 consecutive measurements.
Other reasons for treatment discontinuation are:
• Prolonged lymphopenia at two consecutive weekly visits
• Lymphopenia is defined as < 1000 lymphocytes / µl (< 1.000 * 109 lymphocytes / l) in a whole blood specimen.
• Anaphylactic or other serious allergic reaction
Patients withdrawn from treatment should be followed up for at least 2 additional weeks and should . In case of an AE, the withdrawn patient should be followed up until the AE is resolved or in a steady state.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1

Country: Number of subjects enrolled	Czech Republic: 49
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Latvia: 10
Country: Number of subjects enrolled	Poland: 56
Worldwide total number of subjects	128
EEA total number of subjects	128

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	101
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The Screening period was up to 6 weeks for each subject.
The screening started on 21-DEC-2010 and ended on 04-FEB-2013 (2 year and 2 months). The active sites were in Czech Republic, Germany, Spain, Italy, Poland, Hungary and Latvia.
In total, 128 patients was randomized onto the study. Of which 127 patients received study treatment.

Pre-assignment

Screening details:

Main inclusion criteria: Adult patients (18–75 years, both gender) with active RA (duration of ≥ 12months) with functional class I-III incompletely controlled on methotrexate (MTX), with a history of at least one traditional disease modifying antirheumatic drug (DMARD) with an inadequate response despite ≥ 3 months of treatment and who signed ICF.

Period 1

Period 1 title	Controlled Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

All study staff at the investigational site and study personnel at the sponsor / clinical research organization(s) involved in the conduct of the study remained blinded until study unblinding. Plasma concentrations of BT061 was determined at Biotest only after the blinded data review meeting (BDRM). The independent statistician, independent laboratory specialists and the IDRB members had access to such data before the BDRM. Unblinded personnel were not involved in any analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo group (Group D) received weekly subcutaneous placebo for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2 ml placebo (0 mg/ml BT061) (2 vials) was administered subcutaneously weekly for a 12-week period (in total 12 applications).
The IMP (placebo) was administered by the investigator or designated study staff according to the randomized assigned treatment group.
1 ml of each vial is injected at two different abdominal SC sites. Both SC doses of 1 ml volume each are administered undiluted and slowly in the region of the anterior abdomen into an area of intact skin.1 ml of each vial is injected at two different abdominal SC sites. Both SC doses of 1 ml volume each are administered undiluted and slowly in the region of the anterior abdomen into an area of intact skin.

Arm title	BT061 25 mg

Arm description:

BT061 25 mg Group received weekly subcutaneous 25 mg BT061 for 12 weeks.

Arm type	Experimental

Investigational medicinal product name	BT061 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

25 mg BT061 in 2 ml (1 ml 25mg/ml BT061 + 1 ml placebo 0 mg/ml BT061) was administered subcutaneously weekly for a 12-week period (in total 12 applications).
The IMP (BT061) was administered by the investigator or designated study staff according to the randomized assigned treatment group.
1 ml of each vial is injected at two different abdominal SC sites. Both SC doses of 1 ml volume each are administered undiluted and slowly in the region of the anterior abdomen into an area of intact skin.

Arm title	BT061 50 mg

Arm description:

BT061 50 mg group received weekly subcutaneous 50 mg BT061 for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	BT061 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

50 mg BT061 in 2 ml (1 ml 50 mg/ml BT061 + 1 ml placebo 0 mg/ml BT061) was administered subcutaneously weekly for a 12-week period (in total 12 applications).
The IMP (BT061) was administered by the investigator or designated study staff according to the randomized assigned treatment group.
1 ml of each vial is injected at two different abdominal SC sites. Both SC doses of 1 ml volume each are administered undiluted and slowly in the region of the anterior abdomen into an area of intact skin.

Arm title	BT061 75 mg

Arm description:

BT061 75 mg group received weekly subcutaneous 75 mg BT061 for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	BT061 75 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

75 mg BT061 in 2 ml (1 ml 25 mg/ml BT061 + 1 ml 50 mg/ml BT061) was administered subcutaneously weekly for a 12-week period (in total 12 applications).
The IMP (BT061) was administered by the investigator or designated study staff according to the randomized assigned treatment group.
1 ml of each vial is injected at two different abdominal SC sites. Both SC doses of 1 ml volume each are administered undiluted and slowly in the region of the anterior abdomen into an area of intact skin.

Number of subjects in period 1[1]	Placebo	BT061 25 mg	BT061 50 mg
Started	32	32	32
Completed	28	30	27
Not completed	4	2	5
Consent withdrawn by subject	-	-	1

positive CMV IgM test	-	-	-
patient absence	1	-	-
Adverse event, non-fatal	-	-	2
patient decision to withdraw from treatment	-	-	1
positive EBV IgM test	-	1	-
positive quantiferon test	1	-	1
Protocol deviation	2	1	-
Lack of efficacy	-	-	-

Number of subjects in period 1[1]	BT061 75 mg
Started	31
Completed	27
Not completed	4
Consent withdrawn by subject	2
positive CMV IgM test	1
patient absence	-
Adverse event, non-fatal	-
patient decision to withdraw from treatment	-
positive EBV IgM test	-
positive quantiferon test	-
Protocol deviation	-
Lack of efficacy	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 128 patients were randomized of which 127 patients were treated and included in the APTAS.For patient I0302 (75 mg BT061) the randomization did not lead to treatment due to a system error. Patient I0302 was screened on 16-APR-2012 and, according to the protocol, the Screening period was 6 weeks. On 28 MAY 2012 the 6-week Screening period was exceeded. The sub-investigator tried to randomize the patient on IWRS on time, but she could not because of a problem with IMP in IWRS.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo group (Group D) received weekly subcutaneous placebo for 12 weeks.	
Reporting group title	BT061 25 mg
Reporting group description:	
BT061 25 mg Group received weekly subcutaneous 25 mg BT061 for 12 weeks.	
Reporting group title	BT061 50 mg
Reporting group description:	
BT061 50 mg group received weekly subcutaneous 50 mg BT061 for 12 weeks.	
Reporting group title	BT061 75 mg
Reporting group description:	
BT061 75 mg group received weekly subcutaneous 75 mg BT061 for 12 weeks.	

Reporting group values	Placebo	BT061 25 mg	BT061 50 mg
Number of subjects	32	32	32
Age categorical Units: Subjects			
Adults (18- <40 years)	2	4	5
Adults (40-65 years)	23	21	20
Adults (>65 - 77 years)	7	7	7
Age continuous Units: years			
median	58	54	56.5
full range (min-max)	33 to 75	26 to 71	25 to 76
Gender categorical Units: Subjects			
Female	25	28	29
Male	7	4	3

Reporting group values	BT061 75 mg	Total	
Number of subjects	31	127	
Age categorical Units: Subjects			
Adults (18- <40 years)	4	15	
Adults (40-65 years)	24	88	
Adults (>65 - 77 years)	3	24	
Age continuous Units: years			
median	54		
full range (min-max)	26 to 74	-	
Gender categorical Units: Subjects			
Female	25	107	
Male	6	20	

Subject analysis sets	
Subject analysis set title	All patients treated analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received at least a single dose of study medication (IMP).

Subject analysis set title	Full analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who received at least one dose of IMP and have at least one postbaseline assessment with respect to the efficacy parameters.

Subject analysis set title	Per-protocol (PP) analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

All patients of the full analysis set without any major protocol violations as defined during the blinded data review meeting. Patients with major protocol deviations or incomplete documentation of relevant data will be excluded from the PP analysis.
Patients who miss more than two doses of the IMP do not qualify for the perprotocol analysis set. In any case patients must have received the last two IMP injections of Week 11 and Week 12 to qualify for the PP set.

Subject analysis set title	PK analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients will be considered evaluable for PK analysis if they received at least one dose of BT061, and if they have at least one post-treatment plasma concentration measure of BT061.

Reporting group values	All patients treated analysis set	Full analysis set	Per-protocol (PP) analysis set
Number of subjects	127	127	89
Age categorical Units: Subjects			
Adults (18- <40 years)	15		
Adults (40-65 years)	88		
Adults (>65 - 77 years)	24		
Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female	107		
Male	20		

Reporting group values	PK analysis set		
Number of subjects	127		
Age categorical Units: Subjects			
Adults (18- <40 years)			
Adults (40-65 years)			
Adults (>65 - 77 years)			
Age continuous Units: years median full range (min-max)			

Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo group (Group D) received weekly subcutaneous placebo for 12 weeks.	
Reporting group title	BT061 25 mg
Reporting group description:	
BT061 25 mg Group received weekly subcutaneous 25 mg BT061 for 12 weeks.	
Reporting group title	BT061 50 mg
Reporting group description:	
BT061 50 mg group received weekly subcutaneous 50 mg BT061 for 12 weeks.	
Reporting group title	BT061 75 mg
Reporting group description:	
BT061 75 mg group received weekly subcutaneous 75 mg BT061 for 12 weeks.	
Subject analysis set title	All patients treated analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least a single dose of study medication (IMP).	
Subject analysis set title	Full analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients who received at least one dose of IMP and have at least one postbaseline assessment with respect to the efficacy parameters.	
Subject analysis set title	Per-protocol (PP) analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients of the full analysis set without any major protocol violations as defined during the blinded data review meeting. Patients with major protocol deviations or incomplete documentation of relevant data will be excluded from the PP analysis. Patients who miss more than two doses of the IMP do not qualify for the perprotocol analysis set. In any case patients must have received the last two IMP injections of Week 11 and Week 12 to qualify for the PP set.	
Subject analysis set title	PK analysis set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients will be considered evaluable for PK analysis if they received at least one dose of BT061, and if they have at least one post-treatment plasma concentration measure of BT061.	

Primary: ACR20 response at Week 13

End point title	ACR20 response at Week 13
End point description:	
The primary objective of this study was to investigate dose-response information on efficacy using the ACR20 response criteria after 12 weeks of treatment at study Week 13 (one week after end of treatment). The impact of the IMP on rheumatoid arthritis (RA) disease activity was evaluated by the difference between pre-treatment (baseline) disease activity and one week post-treatment (Week 13) disease activity. An ACR20 response was defined as at least 20% improvement in both the tender joint count and the swollen joint count and at least 20% improvement in 3 of the 5 other core set measures including CRP and/or ESR, Investigator assessment of disease activity, Patient assessment of disease activity, Patient assessment of pain, Health Assessment Questionnaire (HAQ).	
End point type	Primary

End point timeframe:

From baseline to study week 13 (one week after 12 weeks of treatment)

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: subjects				
Response	14	18	18	15
No response	18	14	14	16

End point values	All patients treated analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	127			
Units: subjects				
Response	65			
No response	62			

Statistical analyses

Statistical analysis title	BT061 25 mg versus placebo

Statistical analysis description:

The primary analysis is the final analysis of the 2 groups (BT061 25 mg and placebo) of ACR20 response at Week 13 (using last observation carried forward (LOCF)) which was analysed using logistic regression adjusted for centre effect. The adjusted odds ratio (OR) with 95% confidence interval (CI) and the Wald p-value were calculated for the selected active treatment group against the placebo group together with the significance of the centre effect.

Comparison groups	BT061 25 mg v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	4.44

Notes:

[1] - Wald X2 p-value = 0.3186 and Fisher 2-sided p-value = 0.4536. There was no statistically significant difference in ACR20 response rate versus placebo group.

Statistical analysis title	BT061 50 mg versus placebo

Statistical analysis description:

The primary analysis is the final analysis of the 2 groups (BT061 50 mg and placebo) of ACR20 response at Week 13 (using last observation carried forward (LOCF)) which was analysed using logistic regression adjusted for centre effect. The adjusted odds ratio (OR) with 95% confidence interval (CI) and the Wald p-value were calculated for the selected active treatment group against the placebo group together with the significance of the centre effect.

Comparison groups	BT061 50 mg v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	4.44

Notes:

[2] - Wald X2 p-value = 0.3186 and Fisher 2-sided p-value = 0.4536. There was no statistically significant difference in ACR20 response rate versus placebo group.

Statistical analysis title	BT061 75 mg versus placebo

Statistical analysis description:

The primary analysis is the final analysis of the 2 groups (BT061 75 mg and placebo) of ACR20 response at Week 13 (using last observation carried forward (LOCF)) which was analysed using logistic regression adjusted for centre effect. The adjusted odds ratio (OR) with 95% confidence interval (CI) and the Wald p-value were calculated for the selected active treatment group against the placebo group together with the significance of the centre effect.

Comparison groups	BT061 75 mg v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	3.25

Notes:

[3] - Wald X2 p-value = 0.7121 and Fisher 2-sided p-value = 0.8025. There was no statistically significant difference in ACR20 response rate versus placebo group.

Secondary: ACR50 Response

End point title	ACR50 Response

End point description:

ACR50 response was derived using last observation carried forward and Non-responder Imputation.

An ACR50 response was defined as at least 50% improvement in both the tender joint count and the swollen joint count and at least 50% improvement in 3 of the 5 other core set measures including CRP and/or ESR, Investigator assessment of disease activity, Patient assessment of disease activity, Patient assessment of pain, Health Assessment Questionnaire (HAQ).

End point type	Secondary
End point timeframe:	
From baseline to study Week 13	

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: subjects				
Response	4	7	4	11
No response	28	25	28	20

End point values	All patients treated analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	127			
Units: subjects				
Response	26			
No response	101			

Statistical analyses

Statistical analysis title	BT061 25 mg versus placebo

Statistical analysis description:

The final analysis of the 2 groups (BT061 25 mg and placebo) of ACR50 response at Week 13 (using last observation carried forward (LOCF)) which was analysed using logistic regression adjusted for centre effect. The adjusted odds ratio (OR) with 95% confidence interval (CI) and the Wald p-value were calculated for the selected active treatment group against the placebo group together with the significance of the centre effect.

Comparison groups	BT061 25 mg v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	7.5

Notes:

[4] - Wald X2 p-value = 0.3256 and Fisher 2-sided p-value = 0.5092. There was no statistically significant difference in ACR50 response rate versus placebo group.

Statistical analysis title	BT061 50 mg versus placebo

Statistical analysis description:

The primary analysis is the final analysis of the 2 groups (BT061 50 mg and placebo) of ACR20 response at Week 13 (using last observation carried forward (LOCF)) which was analysed using logistic regression adjusted for centre effect. The adjusted odds ratio (OR) with 95% confidence interval (CI) and the Wald p-value were calculated for the selected active treatment group against the placebo group together with the significance of the centre effect.

Comparison groups	BT061 50 mg v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [5]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	4.4

Notes:

[5] - Wald X2 p-value = 1.0000 and Fisher 2-sided p-value = 1.0000. There was no statistically significant difference in ACR50 response rate versus placebo group.

Statistical analysis title	BT061 75 mg versus placebo

Statistical analysis description:

The primary analysis is the final analysis of the 2 groups (BT061 75 mg and placebo) of ACR20 response at Week 13 (using last observation carried forward (LOCF)) which was analysed using logistic regression adjusted for centre effect. The adjusted odds ratio (OR) with 95% confidence interval (CI) and the Wald p-value were calculated for the selected active treatment group against the placebo group together with the significance of the centre effect.

Comparison groups	BT061 75 mg v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	13.85

Notes:

[6] - Wald X2 p-value = 0.0390 and Fisher 2-sided p-value = 0.0413. There was statistically significant difference in ACR50 response rate versus placebo group.

Secondary: ACR 70 Response

End point title	ACR 70 Response

End point description:

ACR70 response was derived using last observation carried forward and Non-responder Imputation.
An ACR70 response was defined as at least 70% improvement in both the tender joint count and the swollen joint
count and at least 70% improvement in 3 of the 5 other core set measures including CRP and/or ESR, Investigator assessment of disease activity, Patient assessment of disease activity, Patient assessment of pain, Health Assessment Questionnaire (HAQ).

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: subjects				
Response	0	1	1	2
No response	32	31	31	29

End point values	All patients treated analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	127			
Units: subjects				
Response	4			
No response	123			

Statistical analyses

No statistical analyses for this end point

Secondary: Hybrid ACR Scores

End point title	Hybrid ACR Scores

End point description:

The hybrid ACR is derived at each post-baseline visit from the 7 core set items (components: the tender joint count and the swollen joint count and other core set measures including CRP and/or ESR, Investigator assessment of disease activity, Patient assessment of disease activity, Patient assessment of pain, Health Assessment Questionnaire (HAQ)) by the following steps:
1. For each component:
„Bound %change“ = percentage improvement (defined above) provided this is >-100%;
-100% otherwise (Thus, a deterioration can never go beyond -100%.)
2. „Mean %change“ = mean of the 7 „bound %change“ values classified as <20, 20-<50, 50-<70 or 70+.
3. ACR status = „not ACR20“ or „ACR20 but not ACR50“ or „ACR50 but not ACR70“ or „ACR70“ based on the definitions of ACR20, ACR50 and ACR70.

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	32	32	30
Units: scores				
median (full range (min-max))	19.99 (5.8 to 70.0)	37.26 (6.5 to 73.0)	30.30 (-0.1 to 72.7)	29.91 (-62.2 to 70.0)

Statistical analyses

No statistical analyses for this end point

Secondary: DAS28 scores

End point title	DAS28 scores

End point description:

Disease activity score for 28 joints (DAS28) combines information from swollen joints, tender joints, acute phase response, and general health into one continuous measure of RA inflammation. DAS28 criteria are a modified version of DAS, which has a reduced and non-graded joint count. It consists of a 28 tender joint count (range 0 to 28), a 28 swollen joint count (range 0 to 28), ESR, and an optional general health assessment on a VAS (range 0 to 100), which will be assessed for this study.
DAS28 has a continuous scale ranging from 0 to 10. The level of disease activity is interpreted as low (DAS28 ≤ 3.2), moderate (3.2 < DAS28 ≤ 5.1), and high (DAS28 > 5.1). Higher DAS28 scores means worse disease activity.

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: scores				
median (full range (min-max))	5.03 (1.8 to 7.1)	4.25 (1.9 to 7)	4.97 (3.1 to 6.4)	4.91 (1.9 to 7.3)

Statistical analyses

No statistical analyses for this end point

Secondary: EULAR Response

End point title	EULAR Response

End point description:

The EULAR response is defined at each post-baseline visit in terms of Disease Activity Scores (DAS28) change from baseline. If the score is missing it will be derived using LOCF.
If DAS28 at endpoint ≤ 3.2, the response was categorized based on improvement (reduction) in DAS28 from baseline >1.2 (Good), > 0.6 and ≤ 1.2 (Moderate) and ≤ 0.6 (None).
If DAS28 at endpoint > 3.2 and ≤ 5.1, the response was categorized based on improvement (reduction) in DAS28 from baseline >1.2 (Moderate), > 0.6 and ≤ 1.2 (Moderate) and ≤ 0.6 (None).
If DAS28 at endpoint > 5.1, the response was categorized based on improvement (reduction) in DAS28 from baseline >1.2 (Moderate), > 0.6 and ≤ 1.2 (None) and ≤ 0.6 (None).

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: subjects				
Good Response	1	6	1	5
Moderate Response	18	20	20	20
None	13	6	11	6

Statistical analyses

No statistical analyses for this end point

Secondary: CDAI scores

End point title	CDAI scores

End point description:

Clinical Disease Activity Index (CDAI) was calculated at each post-baseline visit as the sum of the number of tender joints (t28) from the 28 joints shaded on the CRF, the number of swollen joints (sw28), the disease activity (patient“s global assessment) and the disease activity (physician“s global assessment).

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: scores				
median (full range (min-max))	22.65 (4.3 to 44.3)	13.05 (1.7 to 46.5)	21.35 (4.7 to 40.6)	18.4 (1.6 to 49.7)

Statistical analyses

No statistical analyses for this end point

Secondary: SDAI Scores

End point title	SDAI Scores

End point description:

The Simplified Disease Activity Index (SDAI) was calculated at each post-baseline visit as the sum of the Clinical Disease Activity Index (CDAI) and the C-reactive protein (CRP) (in mg/dL).
If any components of the SDAI are missing then the score will be missing. If the score is missing it will be derived using LOCF.

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: scores				
median (full range (min-max))	23.8 (4.4 to 47.4)	13.8 (1.8 to 46.8)	21.95 (4.8 to 40.7)	19 (1.7 to 56)

Statistical analyses

No statistical analyses for this end point

Secondary: Tender Joint count change from Baseline

End point title	Tender Joint count change from Baseline

End point description:

Single Component of ACR for RA assesses: 68 joints for tenderness.
Mean levels and percentage changes from baseline were plotted against weeks since start of treatment by treatment group.

Minus percentage changes from baseline means improvement and plus change means worsening.

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: percent change				
arithmetic mean (standard deviation)	-38.71 (± 38.48)	-56.09 (± 31.37)	-47.22 (± 25.67)	-46.16 (± 36.33)

Statistical analyses

No statistical analyses for this end point

Secondary: Swollen Joint Count change from Baseline

End point title	Swollen Joint Count change from Baseline

End point description:

Single Component of ACR for RA assesses: 68 joints for swollenness.
Mean levels and percentage changes from baseline were plotted against weeks since start of treatment by treatment group.

Minus percentage changes from baseline means improvement and plus change means worsening.

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: percent change				
arithmetic mean (standard deviation)	-42.80 (± 34.28)	-67.90 (± 27.28)	-59.89 (± 27.56)	-60.52 (± 37.81)

Statistical analyses

No statistical analyses for this end point

Secondary: C-reactive protein change from Baseline

End point title	C-reactive protein change from Baseline

End point description:

Mean levels of C-reactive protein (CRP in mg/L) and percentage changes from baseline will be plotted against
weeks since start of treatment by treatment group.

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: Percent change				
arithmetic mean (standard deviation)	31.85 (± 179.58)	10.33 (± 83.99)	41.98 (± 160.30)	37.11 (± 154.61)

Statistical analyses

No statistical analyses for this end point

Secondary: ESR change from Baseline

End point title	ESR change from Baseline

End point description:

Erythrocyte Sedimentation Rate (ESR) Mean levels and percentage changes from baseline will be plotted against weeks since start of treatment by treatment group.

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: percent change				
arithmetic mean (standard deviation)	-36.72 (± 32.23)	-43.49 (± 26.62)	-28.08 (± 40.20)	-43.46 (± 33.83)

Statistical analyses

No statistical analyses for this end point

Secondary: Change of VAS for Global Disease Activity (Investigator) from Baseline

End point title	Change of VAS for Global Disease Activity (Investigator) from Baseline

End point description:

Mean levels and percentage changes from baseline for ACR component (VAS for global disease activity (investigator)) will be plotted against
weeks since start of treatment by treatment group.

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: percent change				
arithmetic mean (standard deviation)	-39.49 (± 28.93)	-49.75 (± 32.84)	-40.56 (± 30.18)	-42.11 (± 31.36)

Statistical analyses

No statistical analyses for this end point

Secondary: Change of VAS for Global Disease Activity (Patient) from Baseline

End point title	Change of VAS for Global Disease Activity (Patient) from Baseline

End point description:

Mean levels and percentage changes from baseline for ACR component (VAS for global disease activity (patient)) will be plotted against weeks since start of treatment by treatment group.

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: percent change				
arithmetic mean (standard deviation)	-25.88 (± 27.03)	-19.09 (± 44.67)	-21.55 (± 41.28)	-31.04 (± 43.71)

Statistical analyses

No statistical analyses for this end point

Secondary: Change of VAS for Patient’s Pain from Baseline

End point title	Change of VAS for Patient’s Pain from Baseline

End point description:

Mean levels and percentage changes from baseline for ACR component (VAS for Patient’s Pain) will be plotted against weeks since start of treatment by treatment group.

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: percent change				
arithmetic mean (standard deviation)	-22.48 (± 37.82)	-21.03 (± 39.60)	-25.16 (± 39.23)	-40.27 (± 30.39)

Statistical analyses

No statistical analyses for this end point

Secondary: Change of Health Assessment Questionnaire from Baseline

End point title	Change of Health Assessment Questionnaire from Baseline

End point description:

Mean levels and percentage changes from baseline for ACR component (Health Assessment Questionnaire) will be plotted against weeks since start of treatment by treatment group.

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: percent change				
arithmetic mean (standard deviation)	-20.67 (± 40.62)	-0.63 (± 96.15)	-20.99 (± 32.15)	14.27 (± 196.78)

Statistical analyses

No statistical analyses for this end point

Secondary: Change of FACIT-Fatigue Questionnaire Total Score from Baseline

End point title	Change of FACIT-Fatigue Questionnaire Total Score from Baseline

End point description:

Mean levels and percent changes of Functional Assessment Of Chronic Illness Therapy (FACIT) - Fatigue Questionnaire were plotted against weeks since start of treatment by treatment group.

End point type	Secondary

End point timeframe:

From baseline to study Week 13

End point values	Placebo	BT061 25 mg	BT061 50 mg	BT061 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	31
Units: percent change				
arithmetic mean (standard deviation)	23.57 (± 50.69)	15.19 (± 47.91)	25.51 (± 34.08)	22.25 (± 39.88)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signed informed consent to the end of follow up (up to 30 weeks)

Adverse event reporting additional description:

Only serious nontreatment- emergent AEs that were related to study procedures have been collected. An AE that occurs from the time the patient receives his/her first dose of study drug until his/her final follow up visit, was treatment-emergen AE (TEAE). All TEAEs will be collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	All Patients Treated Analysis Set

Reporting group description:

The All Patients Treated Analysis Set (APTAS) was defined as those patients who are randomised to treatment and receive at least one dose of study medication (BT061 or placebo).
The APTAS has been used for all safety analyses. Patients who received the wrong treatment in error were analyzed as treated for safety analyses.

Reporting group title	Placebo

Reporting group description:

Subjects in Placebo group received sc. 2 ml placebo once weekly (0 mg BT061) for 12 weeks.

Reporting group title	BT061 25 mg

Reporting group description:

Subjects in BT061 25 mg group received sc. 1 ml placebo plus 1 ml BT061 25mg/ml once weekly (25 mg BT061) for 12 weeks.

Reporting group title	BT061 50 mg

Reporting group description:

Subjects in BT061 25 mg group received sc. 1 ml placebo plus 1 ml BT061 50 mg/ml once weekly (50 mg BT061) for 12 weeks.

Reporting group title	BT061 75 mg

Reporting group description:

Subjects in BT061 75 mg group received sc. 1 ml BT061 25mg/ml plus 1 ml BT061 50mg/ml once weekly (75 mg BT061) for 12 weeks.

Serious adverse events	All Patients Treated Analysis Set	Placebo	BT061 25 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 127 (4.72%)	2 / 32 (6.25%)	1 / 32 (3.13%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	1	0	1
Vascular disorders			
Hypertension	Additional description: UNCONTROLLED HYPERTENSION: onset on study day 23, duration of 9 days and resolved. Severity was severe.		

subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Enterocolitis	Additional description: Enterocolitis: onset on study day 142, duration of 6 days and resolved; Severity was moderate.		
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis	Additional description: Acute Gastritis: onset on study day 142, duration of 6 days and resolved; Severity was moderate.		
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis	Additional description: RA EXACERBATION		
subjects affected / exposed	2 / 127 (1.57%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
EXTREMITIES GANGRENE	Additional description: GANGRENE OF TOES OF THE LEFT: onset on study day 157, duration of 9 days and resulted in death. Severity was severe.		
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
PNEUMONIA	Additional description: PNEUMONIA BILATERAL: onset on study day 67, duration of 13 days and resolved. Severity was moderate.		
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	BT061 50 mg	BT061 75 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 32 (3.13%)	2 / 31 (6.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension	Additional description: UNCONTROLLED HYPERTENSION: onset on study day 23, duration of 9 days and resolved. Severity was severe.		

subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enterocolitis	Additional description: Enterocolitis: onset on study day 142, duration of 6 days and resolved; Severity was moderate.		
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis	Additional description: Acute Gastritis: onset on study day 142, duration of 6 days and resolved; Severity was moderate.		
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis	Additional description: RA EXACERBATION		
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
EXTREMITIES GANGRENE	Additional description: GANGRENE OF TOES OF THE LEFT: onset on study day 157, duration of 9 days and resulted in death. Severity was severe.		
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA	Additional description: PNEUMONIA BILATERAL: onset on study day 67, duration of 13 days and resolved. Severity was moderate.		
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All Patients Treated Analysis Set	Placebo	BT061 25 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 127 (62.99%)	20 / 32 (62.50%)	16 / 32 (50.00%)

Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Hypertension			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Pelvic venous thrombosis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Thrombophlebitis superficial			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	4	0	0
Reproductive system and breast disorders			
Spermatocele			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Varicocele			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			

subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Dyspnoea exertional			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Blood albumin decreased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Cytomegalovirus test positive			
subjects affected / exposed	2 / 127 (1.57%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Epstein-Barr virus antibody positive			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Hepatic enzyme increased			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Mycobacteriun tuberculosis complex test positiv			
subjects affected / exposed	5 / 127 (3.94%)	3 / 32 (9.38%)	1 / 32 (3.13%)
occurrences (all)	5	3	1
Protein total decreased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Transaminases increased			

subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Epstein-Barr virus test positive			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 127 (1.57%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	2	1	0
Rib fracture			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Traumatic haematoma			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	8 / 127 (6.30%)	3 / 32 (9.38%)	3 / 32 (9.38%)
occurrences (all)	9	4	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Leukopenia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Sicca syndrome			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Aphthous stomatitis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	2 / 127 (1.57%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Dyspepsia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Glossodynia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	3 / 127 (2.36%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	3	0	1
Steatorrhoea			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Stomatitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			

Ecchymosis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	3 / 127 (2.36%)	2 / 32 (6.25%)	0 / 32 (0.00%)
occurrences (all)	3	2	0
Rash erythematous			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Rash papular			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	2 / 127 (1.57%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	2	0	1
Haemoglobinuria			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Leukocyturia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Back pain			
subjects affected / exposed	6 / 127 (4.72%)	1 / 32 (3.13%)	1 / 32 (3.13%)
occurrences (all)	7	1	1

Bone pain			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Bursitis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Joint swelling			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	3	0	0
Muscle spasms			
subjects affected / exposed	2 / 127 (1.57%)	1 / 32 (3.13%)	1 / 32 (3.13%)
occurrences (all)	2	1	1
Musculoskeletal pain			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Osteopenia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Rheumatoid arthritis			
subjects affected / exposed	8 / 127 (6.30%)	2 / 32 (6.25%)	0 / 32 (0.00%)
occurrences (all)	10	3	0
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Acute tonsillitis			
subjects affected / exposed	2 / 127 (1.57%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	2	0	1
Bronchitis			
subjects affected / exposed	4 / 127 (3.15%)	0 / 32 (0.00%)	2 / 32 (6.25%)
occurrences (all)	4	0	2
Cystitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Cytomegalovirus infection			

subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Dysentery			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Herpes simplex			
subjects affected / exposed	3 / 127 (2.36%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	4	0	0
Herpes zoster			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Laryngitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	12 / 127 (9.45%)	2 / 32 (6.25%)	2 / 32 (6.25%)
occurrences (all)	12	2	2
Oral herpes			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Respiratory tract infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	2 / 127 (1.57%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Sepsis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Tonsillitis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Tooth infection			

subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Tracheitis			
subjects affected / exposed	1 / 127 (0.79%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	BT061 50 mg	BT061 75 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 32 (78.13%)	21 / 31 (67.74%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Thrombophlebitis superficial			

subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	4	0	
Reproductive system and breast disorders			
Spermatocele			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Varicocele			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Dyspnoea exertional			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Blood albumin decreased			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	2	
Cytomegalovirus test positive			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Epstein-Barr virus antibody positive			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Mycobacteriun tuberculosis complex test positiv			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Protein total decreased			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Epstein-Barr virus test positive			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Rib fracture			

subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Traumatic haematoma			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Leukopenia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Sicca syndrome			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Aphthous stomatitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Glossodynia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Steatorrhoea			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Stomatitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Rash erythematous			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Rash papular			

subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Haemoglobinuria			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Leukocyturia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	3 / 32 (9.38%)	1 / 31 (3.23%)	
occurrences (all)	4	1	
Bone pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Bursitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Joint swelling			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	3	
Muscle spasms			

subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Osteopenia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Rheumatoid arthritis			
subjects affected / exposed	2 / 32 (6.25%)	4 / 31 (12.90%)	
occurrences (all)	2	5	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Acute tonsillitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Cystitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Dysentery			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	0	0	
Herpes simplex			
subjects affected / exposed	1 / 32 (3.13%)	2 / 31 (6.45%)	
occurrences (all)	1	3	
Herpes zoster			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	

Laryngitis				
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Nasopharyngitis				
subjects affected / exposed	4 / 32 (12.50%)	4 / 31 (12.90%)		
occurrences (all)	4	4		
Oral herpes				
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Pneumonia				
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)		
occurrences (all)	0	0		
Respiratory tract infection				
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Rhinitis				
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)		
occurrences (all)	1	1		
Sepsis				
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)		
occurrences (all)	0	0		
Tonsillitis				
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)		
occurrences (all)	0	0		
Tooth infection				
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)		
occurrences (all)	0	1		
Tracheitis				
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)		
occurrences (all)	0	0		
Urinary tract infection				
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)		
occurrences (all)	1	0		
Viral infection				
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)		
occurrences (all)	0	1		

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 31 (0.00%) 0	
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 31 (3.23%) 1	
Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 31 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2011	Modification of some Incl./ Excl. criteria, incorporation of non-substantial amendments, refined diagnostic for cronic infectious disease hepatitis B,
15 December 2011	inclusion of two additional substudies for measurement of plasma concentration, numbers of CD3+/ CD4+ lymphocytes, level of CD4 expression,ocupancy of CD4 receptors, measuring the activation of Treg cells and functional capacity of CD4 T cells.
19 January 2012	Batch extension / Placebo
31 August 2012	Optional increase in size of patient population by an additional 0-40 patients in order to obtail sufficient data on PK/PD assessments and T-reg activation prior to interim analysis; PK/ PD assessments are part of the main study, explanation when data on the optional additioanl contingent will be evaluated.
16 October 2013	Cancellation of part II of the study in favour of a lager follow-on trial with a longer treatment duration

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported